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(54) Title: PROTEOGLYCAN COMPOSITIONS FOR TREATMENT OF INFLAMMATORY CONDITIONS

(57) Abstract: Compositions with synergistic anti-inflammatory effects in inflammatory deseases resulting form activation and consequent degranulation of mast cells and followed by secretion of inflammator biomolecules from the activated mast cells, composed of a heavily sulfated, non-bovine proteoglycan such as shark cartilage chondroitin sulfate C, and one or more of a hexosamine sulfate such as D-glucosamine sulfate, a flavone such as quercetin, an unrefined kernel olive oil that increases absorption of these compositions in various routes of administration, S-adenosylmethionine, a histamine-1 receptor antagonist, a histamine-3 receptor agonist, an antagonist of the actions of CRH, caffeine, and a polyamine.

PROTEOGLYCAN COMPOSITIONS FOR TREATMENT OF INFLAMMATORY CONDITIONS

BACKGROUND OF THE INVENTION

The invention is generally related to the treatment of inflammatory conditions. More specifically, the invention is related to compositions containing inhibitors of mast cell activation and secretion such as a proteoglycan that are designed to be used as dietary supplements or adjuvants to conventional approved medications for the relief of inflammatory conditions.

There have been a number of mostly anecdotal reports that the proteoglycan chondroitin sulfate, as well as glucosamine sulfate, a product of the intestinal breakdown of proteoglycans, may be helpful in relieving the pain of osteoarthritis: - Shute N. Aching for an arthritis cure. *US News and World Report,* Feb. 10, 1997.- Cowley G. The arthritis cure? *Newsweek,* Feb. 17, 1997; Foreman J., People, and their pets, tout arthritis remedy. *The Boston Globe*, April 7, 1997; Tye L. Treatment gains scientific attention. *The Boston Globe,* Sep. 25, 2000.

A recent meta-analysis showed potential therapeutic benefit of chondroitin sulfate and/or glucosamine in osteoarthritis [McAlindon *et al. J Am Med Assn.* 283:1469 (2000)], while a double-blind clinical trial with glucosamine showed definite benefits in osteoarthritis with respect to both pain and radiographic joint appearance [Reginster *et al., Lancet* 337:252 (2001)]. However, less than 5% of the chondroitin sulfate in commercially available preparations is absorbed orally, because the size of the molecule and the degree of sulfation impede its absorption from the gastrointestinal tract. Furthermore, such commercial preparations use chondroitin sulfate obtained from cow trachea, with the possible danger of contracting spongiform encephalopathy or "mad cow disease". In fact, the European Union has banned even cosmetics that contain bovine-derived products.

Theoharides *et al.*. *British Journal of Pharmacology* 131:1039 (2000) indicated for the first time how proteoglycans such as chondroitin sulfate may work . The paper reported that chondroitin sulfate and, to a lesser degree, glucosamine sulfate, inhibit activation of mast cells that are known to trigger allergy and asthma. This discovery is the basis for Theoharides, United States patent applications Serial No. 09/056,707, filed April 8, 1998 and 09/773,576, filed February 2, 2001.

Mast cells are also now recognized as important causative intermediary in many painflul inflammatory conditions[Galli, *N Eng J Med.* 328:257 (1993); Theoharides, *Int J Tissue Reactions* 18:1 (1996)], such as insterstitial cystitis and irritable bowel syndrome [Theoharides, *Ann NY Acad, Sci.* 840:619 (1998)], as well as in migraines and possibly multiple sclerosis [Theoharides, *Persp Biol Med.* 26:672 (1983); Theoharides, Life Sci 46:607 (1996)]. In fact, glucosamine was recently considered to be prophylactic for migraines [Russell, *Med Hypoth* 55:195 (2000)].

Mast cells are increasingly implicated in conditions involving inflamed joints, such as in osteoarthritis and rheumatoid arthritis, through activation of local mast cells by, for example, neuropeptides, such as Substance P. Additional indirect evidence also supports the involvement of mast cells in bone resorption: (a) systemic mastocytosis is invariably associated with osteoporosis; (b) inhibition of mast cell mediator release reversed lytic bone changes; (c) depletion of mast cells inhibited bone resorption in organ culture; (d) human synovial mast cells were shown to secrete in response to allergic and non-immunologic stimuli; (e) human mast cells release the cytokine IL-6 and (f) IL-6 has been definitively linked to bone resorption and osteoporosis.

It was recently shown that chondroitin sulfate's ability to inhibit the activation of mast cells compliments the inhibitory effects on mast cell activation of another class of naturally occurring compounds, the flavonoids [Middleton *et al. Pharm Rev* 52:1 (2000)]. Certain plant flavones (in citrus fruit pulp, seeds, sea weed) are now recognized as anti-allergic, anti-inflammatory, anti-oxidant and cytoprotective with possible anti-cancer properties. Only some flavonoids that belong to the subclass of flavones, *e.g.*, quercetin, inhibit mast cell activation.

Quercetin inhibits secretion from human activated mast cells [Kimata *et al. Allergy* 30:501(2000)], and has also been used effectively for the treatment of chronic prostatitis [Shoskes *et al., Urology* 54:960 (1999)]. However, other flavonoids may have opposite effects. Use of the term "bioflavonoids" or "citrus flavonoids" in certain commercial products, therefore, provides little information, and may include molecules that have detrimental effects; for example, soy contains isoflavones that have estrogen-like activity that worsens inflammatory conditions.

Copending United States patent applications Serial Nos. 09/056,707, filed 04/08/98, and divisional 09/773,576 claim the oral use of proteoglycans, without and with flavonoids, for the treatment of mast cell activation-induced diseases. Absorption of these compositions from the gastrointestinal tract and synergism with other treatment modalities were not addressed in these applications.

Applicant has described the use of antagonists of the action of Corticotropin Releasing Hormone (also known as Corticotropin Releasing Factor) in inhibiting myocardial mast cell activation in myocardial ischemia (copending United States patent application Serial No. 08/858,136, filed 05/18/97), in treating stress-induced skin disease (United States Patent No. 6,020,305) and stress-induced migraine headaches (United States Patent No. 5,855,884), the contents of which are incorporated herein by reference. The synergistic effects of the compositions of the present invention that include antagonists of the actions of Corticotropin Releasing Hormone ("CRH") on mast cells were not recognized at the time of the previous studies. The word "antagonists" in connection with CRH is intended herein to include any molecule that prevents the actions of CRH on target cells, and includes, but is not limited to, anti-CRH neutralizing antibodies or binding proteins, or molecules preventing the release of CRH at local sites (see below for details).

Applicant has also described a method for treating patients with mast cell derived molecules-induced interstitial cystitis with histamine-1 receptor antagonists (United States Patent No. 5,994,357). Treatment of mast cell molecules-induced

migraines with histamine-1 receptor antagonists is the subject of Theoharides United States Patent No. 5,855,884. Histamine-3 receptor agonists as pharmaceutical agents in mast cell-involved diseases are described in Theoharides United States Patent No. 5,831,259. The contents of these three patents are incorporated herein by reference. At the time of this invention the synergistic effects of the present compositions with such antagonists had not yet been recognized.

An important need therefore exists for compositions for administration to human patients being treated for mast cell-induced inflammatory diseases by various modalities, that are synergistic in that they have stronger effects than the sum of the effects of the individual components, and also synergistic with conventional clinical treatments of inflammatory conditions. "Synergistic" is also intended to mean: "coordinated or correlated action by two or more structures or drugs" [Stedman's Medical Dictionary, 23rd edition, Williams & Wilkins, Baltimore, 1976]. An important need also exists for formulations that increase the absorption from the gastrointestinal tract, nasal passages and skin surface of the compositions of the invention. Such formulations have been discovered, and are described below.

SUMMARY OF THE INVENTION

The invention comprises compositions for human use containing a sulfated proteoglycan and one or more active ingredients selected from the group consisting of a sulfated hexosamine, a flavonoid compound ("flavone"), an unrefined kernel (seed) olive oil, S-adenosylmethionine ("SAM"), histamine-1 receptor antagonists, histamine-3 receptor agonists, antagonists of the actions of CRH, caffeine and polyamines, together with appropriate excipients and carriers, said compositions having improved absorption from the gastrointestinal tract, skin surface, and nasal and pulmonary surfaces, and anti-inflammatory effects synergistic with each other and synergistic with available conventional clinical treatment modalities.

In one embodiment, the sulfated glucosamine is D-glucosamine sulfate, the proteoglycan is non-bovine chondroitin sulfate, and the flavone is quercetin.

In an other embodiment, compositions may also contain antagonists of the effects of CRH on mast cells or other target cells of the myocardium, gastric mucosa, urinary bladder, skin, meningeal membranes, and blood-brain barrier.

In still another embodiment, the present compositions are used against superficial vasodilator flush syndromes.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS OF THE INVENTION

It has been discovered that a combination of a sulfated proteoglycan, a sulfated D-hexoseamine and a flavone in an unrefined kernel olive oil, with optional CRH antagonists, histamine-1 receptor antagonists, histamine-3 receptor agonists, polyamines and caffeine has synergistic anti-inflammatory effects when used as a dietary supplement, a topical product or an aerosol for nasal or pulmonary adminstration, without or with a conventional clinical treatment for inflammatory diseases. Such inflammatory diseases result from the activation, degranulation and consequent secretion of inflammatory biochemicals from mast cells, and the resultant inflammatory diseases include the group consisting of: allergic inflammation, arthritis (to include osteoarthritis and rheumatoid arthritis), cancer, fibromyalgia, inflammatory bowel disease, interstitial cystitis, irritable bowel syndrome, migraines, angina, chronic prostatitis, eczema, multiple sclerosis, psoriasis, sun burn, periodontal disease of the gums, superficial vasodilator (flush} syndromes and hormonally-dependent cancers.

In a highly preferred embodiment, the sulfated proteoglycan is non-bovine chondroitin sulfate which blocks mast cell activation, degranulation and consequent secretion of inflammatory biochemicals from the mast cells. Other natural sulfated

proteoglycans suitable for practicing this invention include keratan sulfate, dermatan sulfate and hyaluronic acid sodium salt (sodium hyaluronate). The preferred biological source of the chondroitin sulfate is shark cartilage which is more-highly sulfated than the common commercial chondroitin sulfate isolated from cow trachea; the shark cartilage source also avoids the potential dangers associated with bovine sources.

The highly preferred flavone is quercetin which inhibits secretion of inflammatory molecules from mast cells by affecting moesin, a unique 78 kDa mast cell protein [Theoharides *et al. J Pharm Exp Therap* 294:810 (2000)]. In addition to quercetin, other flavones suitable in carrying out the invention include myricetin, genistein and kaempferol.

The kernel olive oil component of the inventive compositions is preferably an unrefined (first pressing, filtered, oleic acid-related acidity <5%, water content <5%) kernel olive oil produced, for one source, on the island of Crete in Greece. This kernel olive oil increases absorption of the other ingredients of the anti-inflammatory compositions, and also adds its own content of important anti-oxidants [Bosku, *World Rev Nutr Diet*, 87:56 (2000)], such as omega fatty acids and alpha tocopherol. Although not claimed herein, it has been claimed that kernel olive oil has cytoprotective, longevity-producing effects [Trichopoulou *et al. Am J Clin Nutr* 61:1346S (1995); Trichopoulou *et al, Cancer Epid Biomarker Prevention* 9:869 (2000)]. The polyphenols in such olive oil also have anti-inflammatory effects in, for example, arthritis [Martinez-Dominguez *et al., Inflamm. Res.* 50:102 (2001)]. A preferred source of the unrefined kernel olive oil of the invention is: E.B.E.K., Inc., Commercial, Industrial Enterprises of Crete, 118 Ethnikis Antistasecos, Heraklion, Crete, 71306, Greece.

Supplementation of the compositions described above with the methylation reagent S-adenosylmethionine ("SAM") adds antioxidant, anti-inflammatory and cytoprotective properties, particularly in inflammatory joint diseases. Addition of SAM also accelcrates metabolism of homocysteine, which has been implicated in coronary disease, to cysteine, which is harmless. Folic acid may be added to certain of the present formulations for similar reasons.

Another supplement to the basic compositions of the invention is a histamine-1 receptor antagonist, such as diphenhydramine, hydroxyzine, azelastine, azatadine and cyproheptadine. Other histamine-1 receptor antagonists are described in Table 25-1 in Goodman and Gilman's The Pharmaceutical Basis of Therapeutics, 9th ed., New York, 1996. Histamine -3 receptor agonists are described in the Theoharides patents listed above.

Inhibitors of mast cell activation and secretion may be used in the treatment of inflammatory processes such as superficial vasodilator syndrome, *e.g.*, menopausal-associated flush, monosodium glutamate-associated flush, carcinoid flush and niacin-associated flush.

Sources of CRH antagonists include, in addition to the Theoharides patents listed in the Background section above: Neurocrine Biochem. Inc.'s D-Phe 12 Nle Ala32,21,38hCRH(12-41)NH2, cat no. 1P-36-41; Pfizer non-peptide CP-154,526-1; Sigma Chem., St. Louis anti-CRH polyclonal antiserum; and Pfizer, NY patents and applications: US6,211,195, US 5,795,905, PCT/IB95/00573, PCT/IB95/00439, US08/448,539, US 08/481,413, US09/735,841, and in Owens *et al. Pharm. Rev.* 43:425 (1991).

The preferred concentration range of the proteoglycan, hexosamine sulfate and flavone components of the oral formulations are 10-3,000 mg per tablet or capsule. The preferred concentration range for SAM is 3-1,000 mg per capsule or tablet. Generally, where present, the amounts of the unrefined kernel olive oil are at least three times those of the other active ingredients, preferably 900-1200 mg. The number of capsules or tablets to be taken per day is determined by the nature and severity of the medical condition, and is readily determinable by the patient's health provider. Other representative formulations are described in the examples below.

The compositions of the invention may be formulated in any standard means of introducing pharmaceuticals parenterally into a patient, e.g., by means of tablets or capsules. The compositions of the invention include ointments and creams for skin

conditions, mouth washes and toothpaste for periodontal diseases, and solutions for nasal aerosols. Standard excipients and carriers for the active ingredients of the inventive compositions are described in Remington's Pharmaceutical Sciences, Mack Publishing Co., Easton, PA.

Although not bound by any particular mechanism of action of the components of the claimed compositions, the inventor contemplates that the proteoglycan inhibits the activation and degranulation of the relevant mast cells, while the flavone inhibits the secretion of inflammatory biomolecules from these mast cells. "Activation" and "degranulation" of mast cells are defined herein as is standard and well known in this art, that is, to mean secretion from the activated mast cell of any type of molecule(s) that alone or in combination triggers inflammatory processes.

EXAMPLES

Example 1

Table 1 compares chondroitin sulfate-containing commercial products to the present compositions.

Table 1

Comparison of Chondroitin Sulfate-Containing Products to Present Invention		
Product	Most Available Compositions	Present Invention
Main ingredient	Mixture of chondroitins	Non-bovine chondroitin sulfate, preferably the C type
Source	Cow trachea	Shark cartilage
Amount per capsule or tablet	100-300	10-3000 mg
Degree of sulfation	Low, if any	High

Absorption from g.i. tract	<5%	>15%
Target	Unknown	Mast cells, inflammatory cells
Other ingredients	Vitamins, fish oils (some preparations)	Flavones, unrefined kernel olive oil, SAM, histamine-1 receptor antagonists, histamine-3 receptor agonists, CRH antagonists, polyamines, caffeine, folic acid
Advantages	None known	Anti-allergic, anti-inflammatory, anti-oxidant, cytoprotective
Adverse effects	Risk of mad cow disease, spongiform encephalopathy, stomach upset, allergy to fish products	None known

Relevant conditions	Osteoarthritis	Allergic inflammation angina, asthma coronary artery disease, arthritis (osteoarthritis or rheumatoid arthritis), chronic prostatitis, eczema, fibromyalgia, interstitial cystitis, irritable bowel syndrome, inflammatory bowel disease, migraines, multiple sclerosis, psoriasis, periodontal disease, flush syndrome, cancer (including hormonally-dependent forms).
Scientific publications	None found	Theoharides *et al. Br J Pharm* 131:1039 (2000) Middleton *et al. Pharm Rev* 52:673 (2000)

* * *

In all examples, chondroitin sulfate is to assumed to be of a non-bovine variety.

Example 2

Composition For Protecting Against Inflammatory Diseases (ALGONOT-PLUS^{R})

Two capsules to be taken orally 2-3 times daily, at least one hour before meals

Ingredients, per capsule,	mg:
* Chondroitin sulfate	150-300
* D-Glucosamine sulfate	150-300
* Quercetin	150-300
* Unrefined kernel olive oil	900-1200

* * *

Example 3

Composition For Protecting Against Arthritis

Ingredients per capsule,	mg:
*D-Glucosamine sulfate	150-300
*Chondroitin sulfate	150-300
*Sodium hyaluronate	100-200
*Quercetin	150-300
*Unrefined kernel olive oil	900-1200

* * *

Example 4

Topical Composition For Protecting Against Arthritis

Skin ointment or cream. Apply three times per day to affected areas.

Ingredients	% by weight
*D-glucosamine sulfate	5
*Condroitin sulfate	5
*Sodium hyaluronate	5
*Bitter willow bark extract	5
*Quercetin	3
*Unrefined kernel olive oil	15

* * *

Example 5

Composition For Protecting Against Cardiovascular Disease

Two capsules to be taken orally 2-3 times per day, in mg:

*Chondroitin sulfate	50
*Kaempferol	100
*S-adenosylmethionine	50
*Niacin	100
*Unrefined kernel olive oil	900-1200

Example 6

Composition For Protecting Against Periodontal Disease

Mouthwash:

*Chondroitin sulfate	0.4 M
*Quercetin	0.4 M

*In a standard mouthwash vehicle

* * *

Example 7

Toothpaste Composition

Toothpaste,	mg%:
*Chondroitin sulfate	5
*Quercetin	3
*Optionally, D-glucosamine sulfate	5

*In a standard toothpaste vehicle

* * *

Example 8

Sunscreen composition

Ingredients	mg%
*Chondroitin sulfate	5
*D-glucosamine sulfate	5
*Quercetin	3
*Sun screen (e.g., TiO_2)	5

* * *

Example 9

Composition For Protecting Against Migraine Headaches

Ingredients,	mg:

*Chondroitin sulfate	50
*Quercetin	100
*Azatadine	4

* Optionally, a CRH-receptor antagonist

* * *

Example 10

Composition For Protecting Against Relapsing Multiple Sclerosis

Ingredients,	mg:
*Chondroitin sulfate	50
*Quercetin	400
*Hydroxyzine	50

*Optionally, interferon-beta

* * *

Example 11

Composition For Protecting Against Cystitis And Prostatitis

Ingredients,	mg:
*D-glucosamine sulfate	50
*Chondroitin sulfate	100-300
*Sodium hyaluronate	200
*Quercetin	100-400
*Unrefined kernel olive oil	900-1200

* * *

Example 12

Composition For Protecting Against "Flush"

Ingredients, per capsule:	
*Chondroitin sulfate	50 mg
*Quercetin	150 mg
*Bitter willow bark extract	5% by weight
*Optionally, cyproheptadine or azatadine	4 mg

* * *

Example 13

Cream Composition For Protecting Against Skin Allergy

Ingredients:	% by weight
*Aloe vera	5
*Non-bovine chondroitin sulfate	5
*Myricetin	5
*Alpha-tocopherol	5
*Unrefined kernel olive oil	15
*Optionally, azelastine or hydroxyzine	5

* * *

Example 14

Composition For Protecting Against Allergy and Allergic Asthma

Ingredients,	mg
Myorcetin	500
Chondroitin sulfate	200
Optionally, azelastine or hydroxyzine	

* * *

Example 15

Composition For Protecting Against Hormonally-Dependent Cancers

Ingredients,	mg
Quercetin	150
Genestein	50
Optionally, tomoxifen or raloxifen	10

* * *

Example 16

Composition For Protecting Against Allergic Conjunctivitis

Ingredients:

***Quercetin**	**0.05%**
*** Chondroitin sulfate**	**2.0%**
***Optionally, azelastine**	**0.05%**

* * *

I claim:

1. A composition with synergistic anti-inflammatory properties in conditions induced by the activation of mast cells, consequent degranulation of said cells and secretion of inflammatory biomolecules, comprising a non-bovine proteoglycan sulfate and one or more of a hexosamine sulfate, a flavone, an unrefined kernel olive oil, S-adenosylmethionine ("SAM"), a histamine-1 receptor antagonist, a histamine-3 agonist, an antagonist of the actions of Corticotropin Releasing Hormone ("CRH"), a polyamine, and caffeine, in an appropriate excipient or vehicle.

2. The composition according to claim 1, wherein said sulfated proteoglycan is selected from the group consisting of non-bovine chondroitin sulfate, keratan sulfate, dermatan sulfate and sodium hyaluronate.

3. The composition according to claim 2, wherein said chondroitin sulfate is chondroitin sulfate C derived from shark cartilage.

4. The composition according to claim 1, wherein said hexosamine sulfate is D-glucosamine sulfate.

5. The composition according to claim 1, wherein said flavone is selected from the group consisting of quercetin, myricetin, genistein and kaempferol.

6. The composition according to claim 1, wherein said unrefined kernel olive oil contains polyphenols and alpha-tocopherol.

7. The composition according to claim 1, said composition being for oral use, comprising 10-3,000 mg per capsule or tablet of each of non-bovine chondroitin sulfate C, quercetin and D-glucosamine sulfate, with 900-1200 mg unrefined kernel olive oil.

8. The composition according to claim 7, further supplemented with 3-1,000 mg of SAM per capsule or tablet.

9. A composition according to claim 1, wherein said inflamatory diseases are selected from the group consisting of: arthritis, cancers, fibromyalgia, inflammatory bowel disease, interstitial cystitis, irritable bowel syndrome , migraines, angina, chronic prostatitis, eczema, multiple sclerosis, psoriasis, sun burn, tooth decay, periodontal disease, stressed-induced migraines, stress-induced opening of bladder mucosa, stress-induced opening of the blood-brain barrier, superficial vasodilator(flush} syndrome, and hormonally-dependent cancers.

10. The composition according to claim 9, wherein said inflammatory disease is

arthritis and said composition is for oral administration, comprising non-bovine chondroitin sulfate, quercetin, D-glucosamine sulfate, unrefined kernel olive oil, and, optionally, sodium hyaluronate.

11. The composition according to claim 9, wherein said inflammatory disease is arthritis and said composition is for topical use, comprising D-glucosamine sulfate, non-bovine chondroitin sulfate, sodium hyaluronate, bitter willow bark extract, quercetin and unrefined kernel olive oil.

12. The composition according to claim 9 for oral or aerosol use in allergic conditions, comprising non-bovine chondroitin sulfate and a flavonoid selected from the group consisting of quercetin, myricetin and kaempferol, unrefined kernel olive oil, and, optionally, a histamine-1 receptor antagonist.

13. The composition according to claim 9, for topical use in allergic conditions, comprising non-bovine chondroitin sulfate, myricetin, alpha-tocopherol, unrefined kernel olive oil, and, optionally, a histamine-1-receptor antagonist.

14. The composition according to claim 13, wherein said antagonist is diphenhydramine, hydroxyzine, azatadine, azelastine or cyproheptadine

15. The composition according to claim 9 wherein said inflammatory disease is superficial vasodilator "flush" syndrome, said composition comprising a non-bovine proteoglycan, a flavonoid, bitter willow bark extract, and, optionally, cyproheptadine or azatadine.

16. The composition according to claim 9, wherein said inflammatory disease is multiple sclerosis, said composition comprising quercetin or myricetin, hydroxyzine, and, optionally, caffeine, SAM and interferon-beta.

17. The composition according to claim 9, wherein said inflammatory disease is migraine headaches, and said composition comprises non-bovine chondroitin sulfate, quercetin, and azatadine

18. The composition according to claim 1, said composition being for oral use, comprising 150-300 mg per capsule or tablet of each of non-bovine chondroitin sulfate, quercetin and D-glucosamine sulfate, with 900-1200 mg of unrefined kernel olive oil, and, optionally, 100-200 mg sodium hyaluronate and/or 100 mg SAM.

19. The composition according to claim 1, said composition consisting of an ointment or cream for topical application, comprising, in % by weight, non-bovine

chondroitin sulfate, 5; D-glucosamine sulfate, 5; quercetin, 3; sodium hyaluronate 5; bitter willow bark extract 5; and unrefined kernel olive oil, 15.

20. The composition according to claim 19 supplemented by at least one of the histamine-1 receptor antagonists diphenhydramine, hydroxyzine, azelastine, azatadine r cyproheptadine, 1-5 mg %.

21. The composition according to claim 1, said composition compromising a mouth wash composition, consisting of non-bovine chondroitin sulfate and quercetin, each 0.3-0.4 M, and, optionally, at least one of D-glucosamine sulfate, 0.4 M and SAM, 0.15 M, in a mouth wash vehicle.

22. The composition according to claim 1, said composition consisting of a tooth paste, comprising, in mg%, non-bovine chondroitin sulfate, 5; quercetin, 3; and, optionally, D-glucosamine sulfate, 5, in a tooth paste vehicle.

23. The composition according to claim 1, said composition consisting of a sunscreen composition, comprising , in mg% , non-bovine chondroitin sulfate, 5; quercetin 3; and at least one of D-glucosamine sulfate, 5, and titaniun dioxide, 5, in a sun screen vehicle.

24. The composition according to claim 1, for use in treating migraine headaches, said composition comprising, in mg, non-bovine chondroitin sulfate, 50 ; guercetin, 100 ; azatadine ,4; and, optionally, a CRH antagonist.

25. The composition according to claim 1, said composition comprising, in mg, non-bovine chondroitin sulfate, 50: quercetin, 400; hydroxyzine, 50; and, optionally, a CRH antagonist.

26. The composition according to claim 1, said composition comprising, in mg, non-bovine chondroitin sulfate, 100; D-glucosamine sulfate, 50; quercetin, 100; and unrefined kernel olive oil, 900-1200.

27 . The composition according to claim 1, comprising, in mg%, non-bovine chondroitin sulfate, 5; D-glucosamine sulfate, 5; quercetin, 3; in 900-1200 mg of unrefined kernel olive oil.

28. The composition according to claim 1, wherein said inflammatory disease is cancer and wherein said composition is designed for oral use, comprising 25-50 mg of genistein and 150-300 mg of quercetin, in 900-1200 mg unrefined kernel olive oil.

29. The composition according to claim 1, wherein said inflammatory disease is

atherosclerosis with or without myocardial ischemia, comprising 100-300 mg each of non-bovine chondroitin sulfate , myricetin, folic acid and SAM, in 900-1200 mg unrefined kernel olive oil, in a vehicle for oral use.

30. The composition according to claim 1, wherein said inflammatory disease is interstitial cystitis or prostatitis, said composition comprising, in mg, 100-300 of non-bovine chondroitin sulfate, 50-300 D-glucosamine sulfate, 100-300 of sodium hyaluronate, and 100-400 quercetin, 900-1200 unrefined kernel olive oil, in a vehicle for oral use.

31. The composition according to claim 1, wherein said inflammatory disease is multiple sclerosis, said composition comprising, in mg, 50-300 each of non-bovine chondroitin sulfate, myricetin, hydroxyzine and SAM, 900-1200 of unrefined kernel olive oil, and, optionally, interferon-beta, in a vehicle for oral use.

32. The composition according to claim 1, said composition comprising, in mg, non-bovine chondroitin sulfate 500; myricetin 300; and diphenhydramine, 5 mg%.

33. The composition according to claim 1, said composition comprising, in mg, non-bovine chondroitin sulfate, 50; kaempferol, 100; SAM, 50; folic acid, 50; niacin, 100; and unrefined kernel olive oil, 900-1200.

34. The composition according to claim 1, wherein said inflammatory disease is superficial vasodilation flush syndrome, said composition comprising 50 mg non-bovine chondroitin sulfate, 150 mg quercetin, 5% by weight bitter willow bark extract, and, optionally, 4 mg cyproheptadine or azatadine.

35. The composition according to claim 1, wherein said inflammatory disease is skin allergy, said composition comprising, in % by weight, 5 each of aloe vera, non-bovine chondroitin sulfate and alpha-tocopherol, 15 of unrefined kernel olive oil, and, optionally, azelastine.

36. The composition according to claim 1, wherein said inflammatory disease in allergy or allergic asthma, comprising 500 mg of myricetin, 200 mg of chondroitin sulfate, and, optionally, azelastine or hydroxyzine.

37. The composition according to claim 36, in an aerosol vehicle.

38. The composition according to claim 1, wherein said inflammatory disease is a hormonally-dependent cancer, comprising, in mg, 150 quercetin, 50 genestein, and, optionally, 10 tamoxifen or raloxifen.

39. The composition according to claim1, wherein said inflammatory disease is allergic conjunctivitis, comprising quercetin 0.05%, chondroitin sulfate 2.0%, and, optionally, azelastine 0.05%.

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